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EXAMINER	
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Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Part III DETAILED ACTION

1. Claims 106-112 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this section can be found in a prior Office action.

3. The copy of the 1449 dated 4 February 1994 is being provided with the instant Office action.

Priority

4. The claimed invention is not deemed to have priority to the earlier applications, as requested by the Applicant, because the claims are not enabled under 35 USC § 112, first paragraph.

Claim Rejections - 35 USC § 112

5. The objection to the specification and rejection of claim 110 under 35 USC § 112, first paragraph, set forth in paragraph 7 of the previous Office action is maintained. Although applicant has provided a written description of a method for selecting the claimed monoclonal antibody, this method will not necessarily reproduce the antibody and hybridoma which are chemically and structurally identical to those claimed. The specification discloses the DNA and amino acid sequences of the cA2 light chain variable region in Figure 17A and SEQ ID No. 2 and 3. The nucleic acid and amino acid sequences shown in Figure 17B, which correspond to SEQ ID No. 4 and 5 are identified in the Brief Description of the Drawings as corresponding to constant region sequences of cA2. The sequence of the heavy chain variable region of the cA2 monoclonal antibody is not disclosed. It is unclear that one of skill in the art could derive a monoclonal antibody identical the cA2 antibody claimed based on the description in the specification. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibody and cell line. Because one of skill in the art could not be assured of the ability to practice the invention as claimed, in the absence of the availability of a cell line that produces the claimed antibody, a suitable deposit for patent purposes, evidence of public availability of the cell line that produces the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibodies, is required. See CFR 1.801 - CFR 1.809. Upon compliance with the deposit requirement set forth above, amendment to claim 110 to recite the depository accession number of the cell line which produces monoclonal cA2 is requested.

6. The specification is objected to under 35 U.S.C. § 112, first paragraph as discussed in the previous Office action and for the reasons discussed below, as failing to provide an enabling disclosure.

The specification is objected to with regards to the subject matter of newly amended claims 106-112 pertaining to methods of treating TNF-alpha mediated diseases. The claims are drawn to a method of treating TNF-alpha mediated diseases in a human comprising administering an anti-TNF chimeric antibody. Claims are further drawn to chimeric antibodies that bind particular epitopes and further to the chimeric antibody cA2. The claimed invention is not enabled for the scope of the TNF-alpha mediated diseases encompassed by the claims based on the unpredictability in the art and lack of guidance provided by the specification. For example, the specification fails to enable one of skill in the art how to make and use an anti-TNF-alpha antibody for use in preventing and treating septic shock. The state of the art was, at the time the invention was made, and still is unpredictable with regards to making and using anti-TNF-alpha antibodies for use in treating septic shock. Natanson et al. (Annals of Internal Medicine, 1994) teach that TNF alpha binding proteins have not been shown to improve outcome in the treatment of human sepsis and septic shock and may, in fact, be potentially harmful. Natanson et al. goes on to teach "Identification of patients in whom an exaggerated cytokine response develops and who are thus likely to benefit from anti-inflammatory treatment strategies remains an important issue. The timing, duration, and delivery of these therapies to tissue compartments (to the peritoneum or lung, for example) are other critical unresolved issues. Clearly, suppression of cytokine function may be injurious for some patients, and that effect of these agents on bacterial clearance, nosocomial infection, and the reparative processes after tissue damage from sepsis requires further investigation. Whether it is clinically feasible to inhibit cytokines and limit their harmful effects while preserving their ability to perform necessary beneficial functions is unknown. The lack of efficacy in four clinical trials and harm produced by one TNF antagonist prompts questions about the methodology used, the viability of this therapeutic approach, or both." See pp.774-777, p.776 column 2 in particular.

Therefore, it is clear that the art teaches that the results from animal models of septic shock cannot be extrapolated to humans. Furthermore, the specification does not teach identifying patients who would benefit from treatment and the timing, duration and delivery of the compositions to humans that would benefit the patient without producing harm. Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method of treating TNF-alpha

mediated diseases using a composition comprising anti-TNF-alpha chimeric antibodies.

7. Claims 106-112 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 103

8. Claims 106-112 are rejected under 35 U.S.C. § 103 as being unpatentable over Shalaby et al. (U) or Brennan et al. (V) or Buurman (U.S. Patent No. 5,183,657) in view of Moller et al. (U.S. Patent No. 5,231,024 or Cytokine, 1990) or Rathjen et al. (WO 91/02078) and Morrison et al. (Science, 1985, 225:1202-1207).

The claims are drawn to a method of treating TNF-alpha mediated disease in a human comprising administering an anti-TNF chimeric antibody. Claims are further drawn to chimeric antibodies that bind particular epitopes and further to a chimeric antibody cA2.

Shalaby et al. (U) teaches a method of using anti-TNF-alpha antibodies to prevent graft-verses-host disease (GVHD) in mice. Shalaby et al. suggests that antibodies to TNF-alpha may be a useful adjuvant for the treatment of GVHD in humans (discussion last paragraph in particular).

Brennan et al. (V) teach a method of using anti-TNF-alpha antibodies to prevent IL-1 production in mononuclear cells from patients with rheumatoid arthritis and suggest that injection of anti-TNF-alpha antibodies locally into a rheumatoid joint may be a useful therapy in severe rheumatoid arthritis (p.244, introduction and p. 246 second column in particular).

Buurman (U.S. Patent No. 5,183,657) teach a method of using anti-TNF-alpha antibodies to prevent shock in humans caused by antilymphocyte antibody therapy (col. 1 and 2 in particular). Shalaby et al., Brennan et al. and Buurman do not teach chimeric anti-TNF chimeric antibodies.

The Moller et al. references teach a method of using the monoclonal antibody M195 which appears to be the same as the antibody of the present invention. M195 is functionally similar to the A2 antibody as characterized in the specification, in exhibiting high affinity binding to TNF-alpha, neutralizing TNF-alpha but not TNF-beta (see p. 164 Table 2, Cytokine) binding to human and chimpanzee TNF but not TNF from baboon, rhesus monkey or cynomolgus monkey (e.g. cytokine, p164 col. 1). In view of those similarities, the A2 and M195 antibodies appear to have the same or similar epitope binding specificities and M195 is expected to have the properties recited in the instant claims. Moller et al. does not teach chimeric anti-TNF-alpha antibodies.

WO 9102078 teaches high affinity TNF-specific antibodies which bind to neutralizing epitopes. Certain of these antibodies bind to epitopes located within synthetic peptides corresponding

to TNF-alpha, which contain an epitope recognized by the A2 antibody. According to the teaching of the specification the A2 antibody binds to synthetic peptides comprising residues 87-108 and 59-80. According to the teaching on page 33 of the reference, Mab 1 binds to a peptide consisting of residues 58-65, Mab 11 binds to a peptide consisting of residues 49-98, Mab 42 binds to a peptide consisting of residues 49-96, Mab 54 binds to a peptide consisting of residues 56-79, etc. Results of competitive binding assays using the referenced antibodies are shown in Fig 9. The antibodies are shown to inhibit biological activities of TNF-alpha according to the teaching in Table 2 , page 22. At least some of the referenced antibodies would be expected to competitively inhibit binding of Mab A2 of the instant invention to TNF-alpha and to have the ID50 values recited in the claims. Rathjen et al. does not teach chimeric anti-TNF-alpha antibodies.

Morrison teaches that chimeric antibodies were considered to be superior to rodent antibodies for use in in vivo therapies and teach that methods for producing chimeric antibodies were well established in the art at the time the invention was made (p.1207 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to chimerize the antibodies of Moller et al. (U.S. Patent 5,231,024 or Cytokine, 1990) using the method Morrison et al. (Science, 1985) for the treatment GVHD as taught by Shalaby et al. or rheumatoid arthritis as taught by Brennan et al. or antilymphocyte antibody induced shock as taught by Buurman. One of ordinary skill in the art at the time the invention was made would have been motivated to chimerize the antibodies of Moller et al. to prevent human anti-mouse antibody antibodies (HAMA).

It is known in the art that murine antibodies have characteristics which may severely limit their use in human therapy. As foreign proteins, murine antibodies may elicit immune reactions that reduce or destroy their therapeutic efficacy and/or evoke allergic or hypersensitivity reactions in patients. The probable need for re-administration of such therapeutic modalities in one of the above disorders increases these risks. Further tissue injury could occur by virtue of antigen-antibody deposition.

The claimed antibodies do not appear to differ in any unexpected or unobvious manner from those that one of ordinary skill in the art would have expected to obtain in view of the teachings of Moller or Rathjen et al. in combination with Morrison. Applicant has presented no evidence which is supportive of a conclusion that the claimed chimeric antibodies differ in any unexpected or unobvious manner from those that would have been suggested by the combined teachings of Moller or Rathjen et al. in combination with Morrison.

9. Applicant's arguments with respect to the Lichtenstein, Sun et al. and Le references have been considered but are deemed to be moot in view of the new grounds of rejection necessitated by Applicant's claim amendments.

10. Applicant's arguments to the use of the Moller and Rathjen references filed 7/10/96 have been fully considered but they are not deemed to be persuasive. Applicant argues that the Moller and Rathjen references do not explicitly describe the epitopic specificity of the disclosed monoclonal antibodies.

Although Moller does not specifically delineate the sequences of TNF-alpha which contain the M195 epitope, the functional characterization of M195 in the references establishes that the M195 of Moller and the A2 antibody of the invention are functionally similar. Both antibodies bind to human and chimpanzee TNF-alpha and neutralize TNF-alpha biological activity and fail to bind to rat, rabbit, dog, pig, baboon, rhesus and cynomolgus TNF-alpha. The prior art M195 monoclonal antibody is so functionally similar to the A2 antibody of the present invention as to suggest that the M195 and A2 antibodies recognize the same epitope or at least a closely related epitope such that the M195 monoclonal antibody would competitively inhibit binding of Mab A2.

Rathjen et al. teach ligands which are specific for human TNF-alpha and which neutralize various biological activities of TNF-alpha. Among the antibodies taught are antibodies which bind to an epitope comprising residues within the region of amino acids 96-105 of TNF-alpha (see p. 10, line 23 in particular), which is within the region of amino acids 87-108 recited in claim 111. Monoclonal antibodies Mab12 and Mab54 are disclosed on page 33 as binding to sites on TNF-alpha exclusive of the amino acids recited in claim 6. Rathjen et al. disclose on page 4 that ligands according to their invention include antibodies and humanized antibodies. Given the proximity of the binding sites of certain of the referenced antibodies to that of the A2 antibody of the present invention it is reasonable to presume that at least some of the referenced antibodies would competitively inhibit binding of the A2 antibody.

No claims are allowable.

11. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION

IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Lucas whose telephone number is (703) 305-6838. The examiner can normally be reached on M-T from 8:00am to 6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311. The fax phone number for this Group is (703) 305-7362 or 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John Lucas, PhD

20 August 1996

LILA FEISEE
PRIMARY EXAMINER
GROUP 1800